Generation of functional lungs via conditional blastocyst complementation using pluripotent stem cells.

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Public Summary:
Millions of people worldwide with incurable end-stage lung disease die because of inadequate treatment options and limited availability of donor organs for lung transplantation. Current bioengineering strategies to regenerate the lung have not been able to replicate its extraordinary cellular diversity and complex three-dimensional arrangement, which are indispensable for life-sustaining gas exchange. Here we report the successful generation of functional lungs in mice through a conditional blastocyst complementation (CBC) approach that vacates a specific niche in chimeric hosts and allows for initiation of organogenesis by donor mouse pluripotent stem cells (PSCs). We show that wild-type donor PSCs rescued lung formation in genetically defective recipient mouse embryos unable to specify (due to Ctnnb1cnull mutation) or expand (due to Fgfr2cnull mutation) early respiratory endodermal progenitors. Rescued neonates survived into adulthood and had lungs functionally indistinguishable from those of wild-type littermates. Efficient chimera formation and lung complementation required newly developed culture conditions that maintained the developmental potential of the donor PSCs and were associated with global DNA hypomethylation and increased H4 histone acetylation. These results pave the way for the development of new strategies for generating lungs in large animals to enable modeling of human lung disease as well as cell-based therapeutic interventions.

Scientific Abstract:
Millions of people worldwide with incurable end-stage lung disease die because of inadequate treatment options and limited availability of donor organs for lung transplantation(1). Current bioengineering strategies to regenerate the lung have not been able to replicate its extraordinary cellular diversity and complex three-dimensional arrangement, which are indispensable for life-sustaining gas exchange(2,3). Here we report the successful generation of functional lungs in mice through a conditional blastocyst complementation (CBC) approach that vacates a specific niche in chimeric hosts and allows for initiation of organogenesis by donor mouse pluripotent stem cells (PSCs). We show that wild-type donor PSCs rescued lung formation in genetically defective recipient mouse embryos unable to specify (due to Ctnnb1(cnull) mutation) or expand (due to Fgfr2(cnull) mutation) early respiratory endodermal progenitors. Rescued neonates survived into adulthood and had lungs functionally indistinguishable from those of wild-type littermates. Efficient chimera formation and lung complementation required newly developed culture conditions that maintained the developmental potential of the donor PSCs and were associated with global DNA hypomethylation and increased H4 histone acetylation. These results pave the way for the development of new strategies for generating lungs in large animals to enable modeling of human lung disease as well as cell-based therapeutic interventions(4-6).